Sinalização Redox e Mecanismos Adaptativos

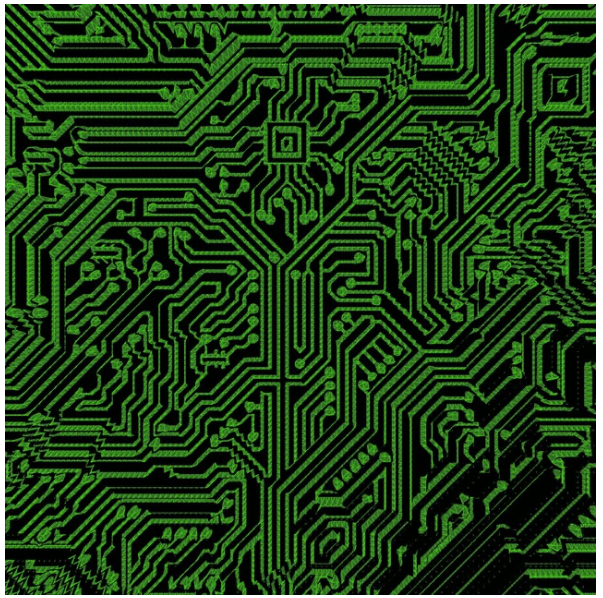
QBQ2509: Bioquímica Redox
QBQ5893: Processos Redox em Bioquímica

Dr. Danilo B. Medinas

Material de estudo para prova

Halliwell: Capítulo 5

Manuscritos citados

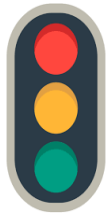


Integração da informação biológica

Tópicos e metas da aula

- **Considerações sobre sinalização celular.**
  - Entender a lógica ou estruturação da comunicação de processos biológicos entre o ambiente e a célula, entre células e dentro da célula (entre organelas).
- **Indícios para o papel de oxidantes em respostas biológicas.**
  - Reconhecer marcos históricos e evidencias experimentais que contribuíram para a concepção de sinalização redox.
- **Tipos de oxidantes que podem funcionar como mensageiros.**
  - Conhecer os requerimentos termodinâmicos e cinéticos para a evolução de espécies redox como sinalizadores moleculares.
- **Mecanismos bioquímicos da sinalização redox e fontes celulares de oxidantes.**
  - Compreender como a especificidade da informação transmitida é atingida e as implicações biológicas da sinalização redox.

Sinalização celular

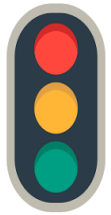


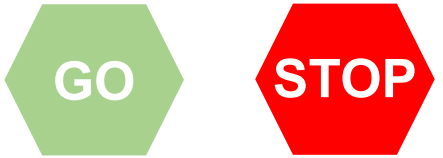
Estímulo → **Transdutor de sinal** → **Mensageiro** → **Efetor** → **Alvo biológico** → **Resposta**

Características:

- ✓ Especificidade
- ✓ Cinética rápida
- ✓ Reversibilidade

Sinalização redox





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Estímulo redox
Transdutor redox
Mensageiros redox
Efetores redox
(centros metálicos; Cys; Met; SelCys)

The Nobel Prize in Physiology or Medicine 1998

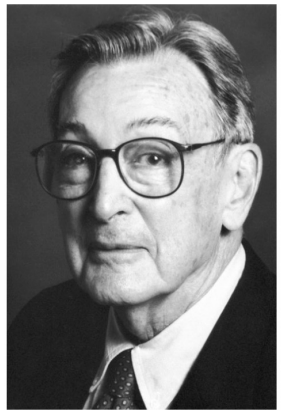
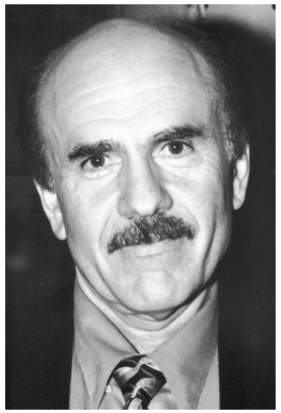


Photo from the Nobel Foundation archive.

Robert F. Furchgott

Prize share: 1/3



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Louis J. Ignarro

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Ferid Murad

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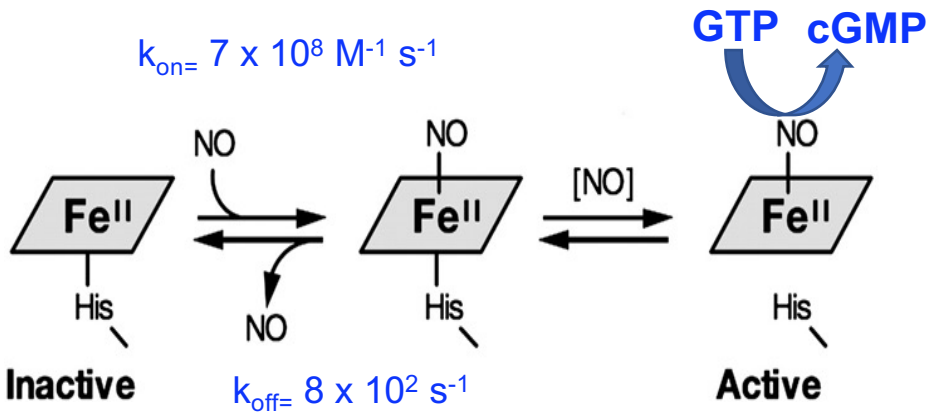
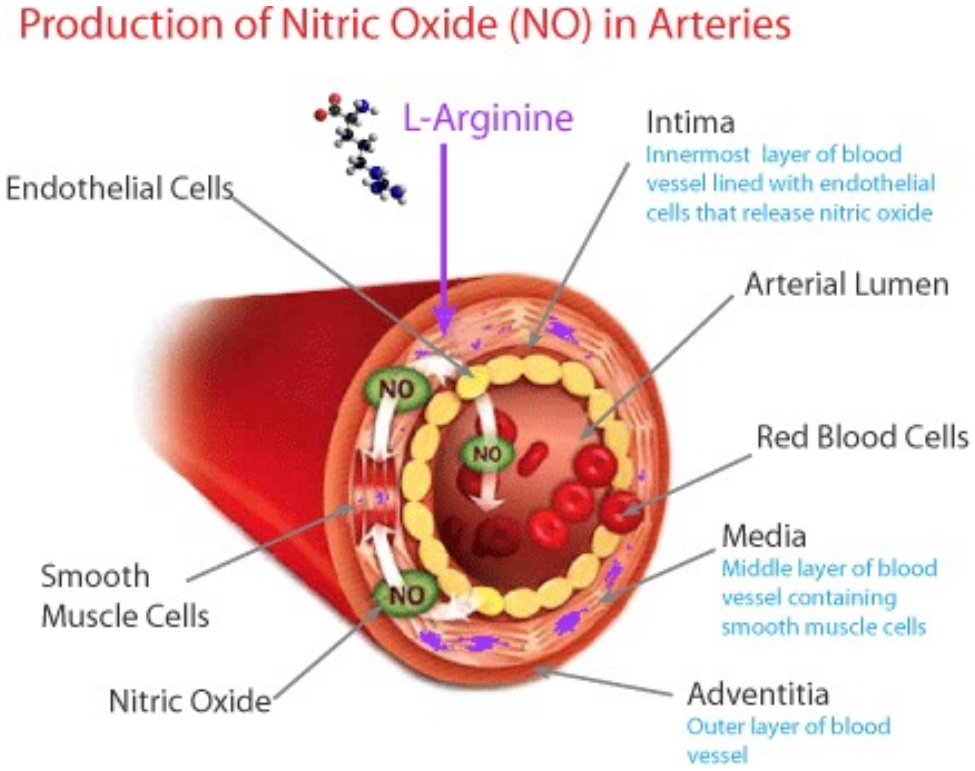
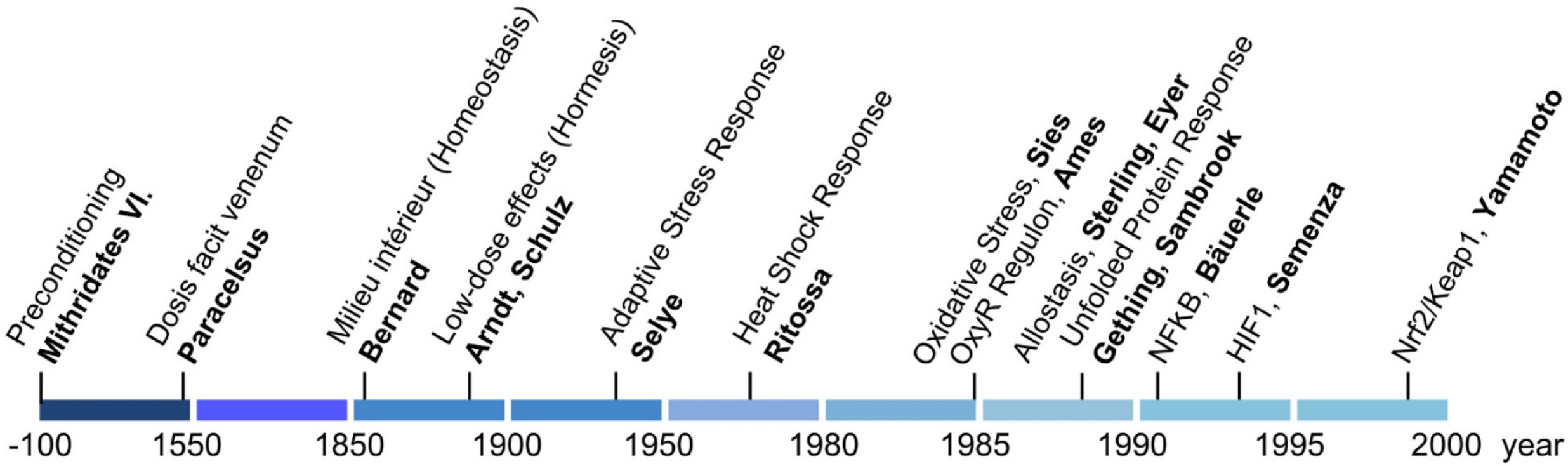


Toledo e Augusto, CRT, 2012



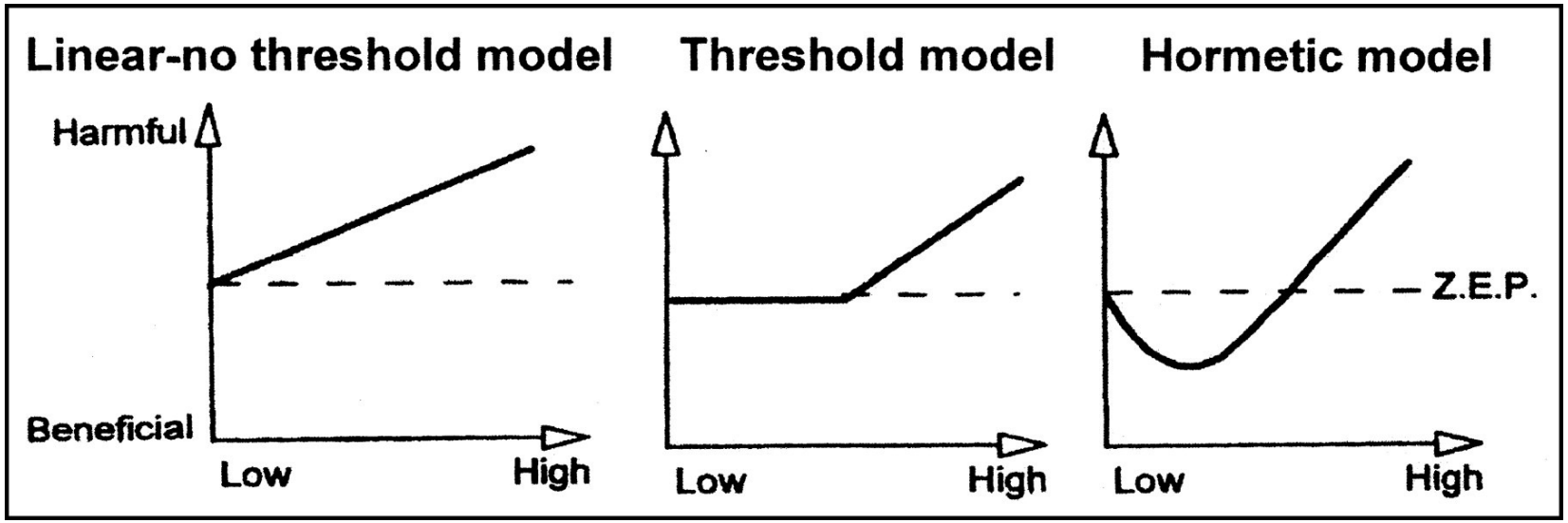
https://wholehealthathome.com/importance-nitric-oxide/

Respostas ao estresse – perspectiva no tempo



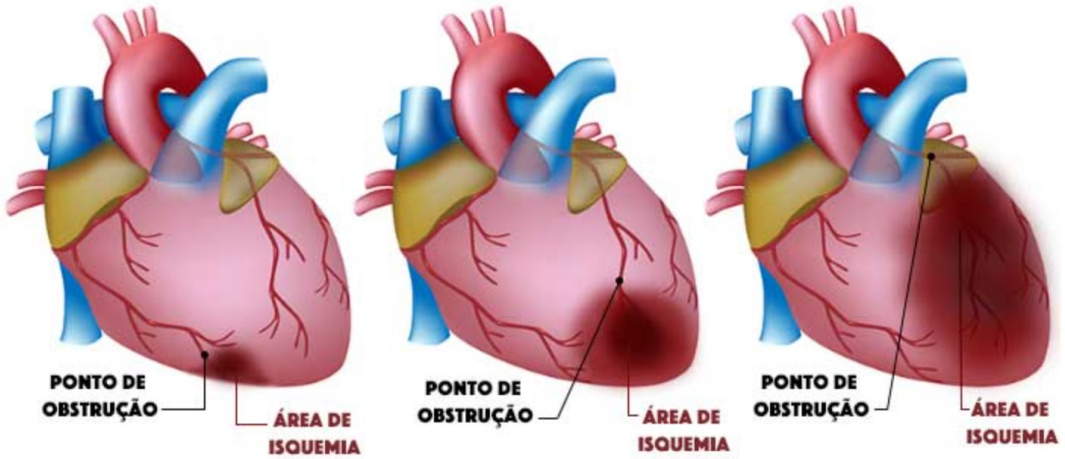
Sies, Redox Biology, 2021

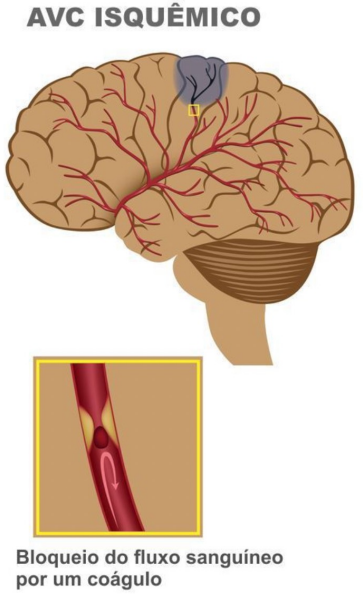
Hormese

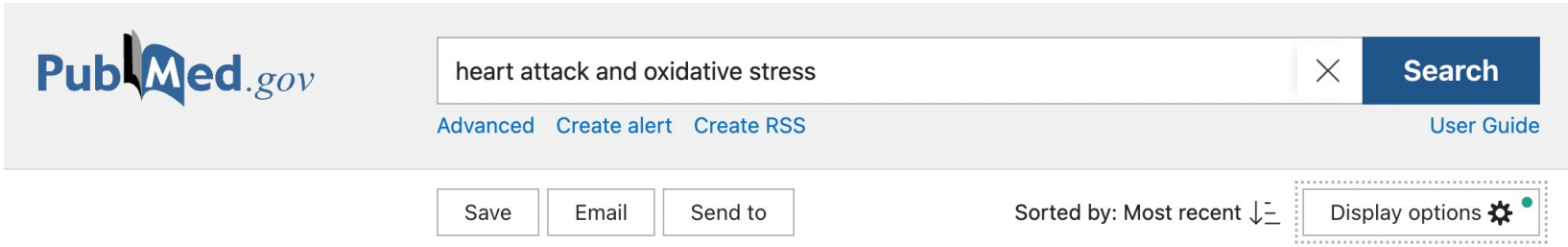


Prekeges, J Nucl Med Tech, 2003

Infarte do Coração e Derrame Cerebral



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heart attack and oxidative stress
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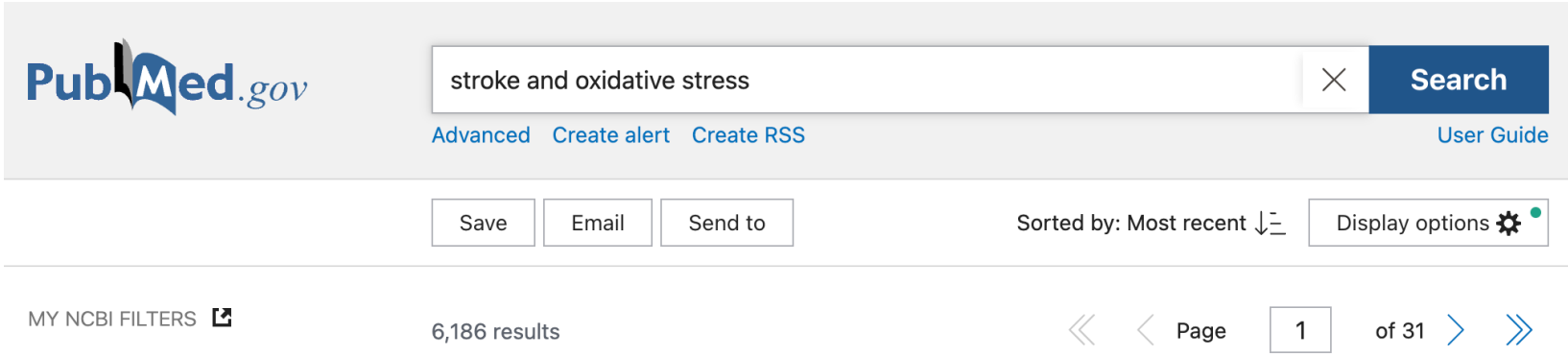
of 19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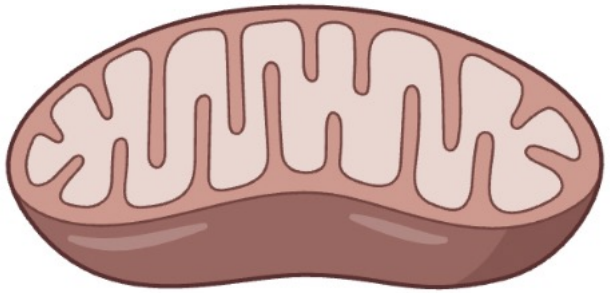
of 31

Estresse Oxidativo na Reperfusão

Xantina Oxidase

Hipoxantina —XO→ Xantina —XO→ Ácido Úrico

O_2 → $\cdot O_2^-$; O_2 → $\cdot O_2^-$

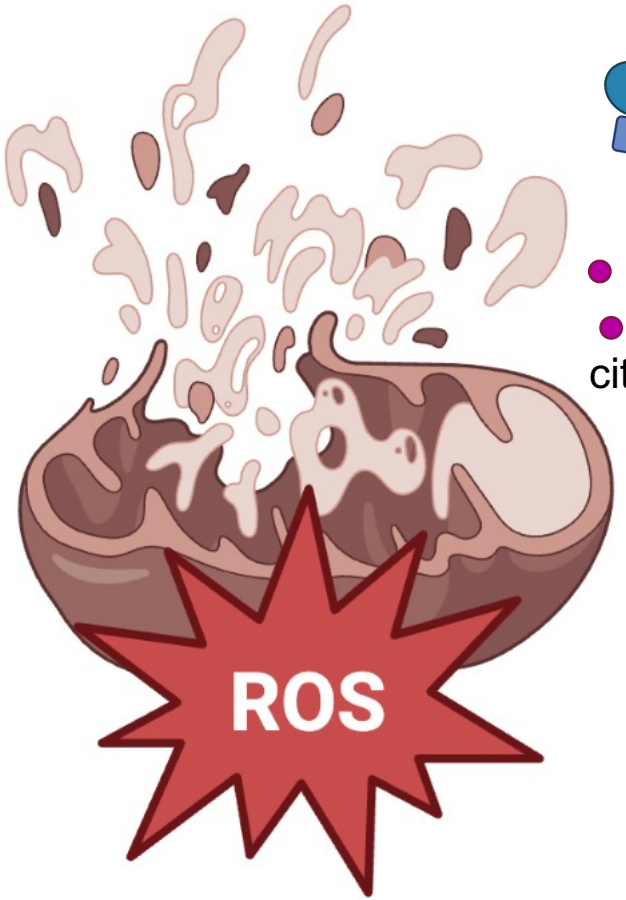


Isquemia

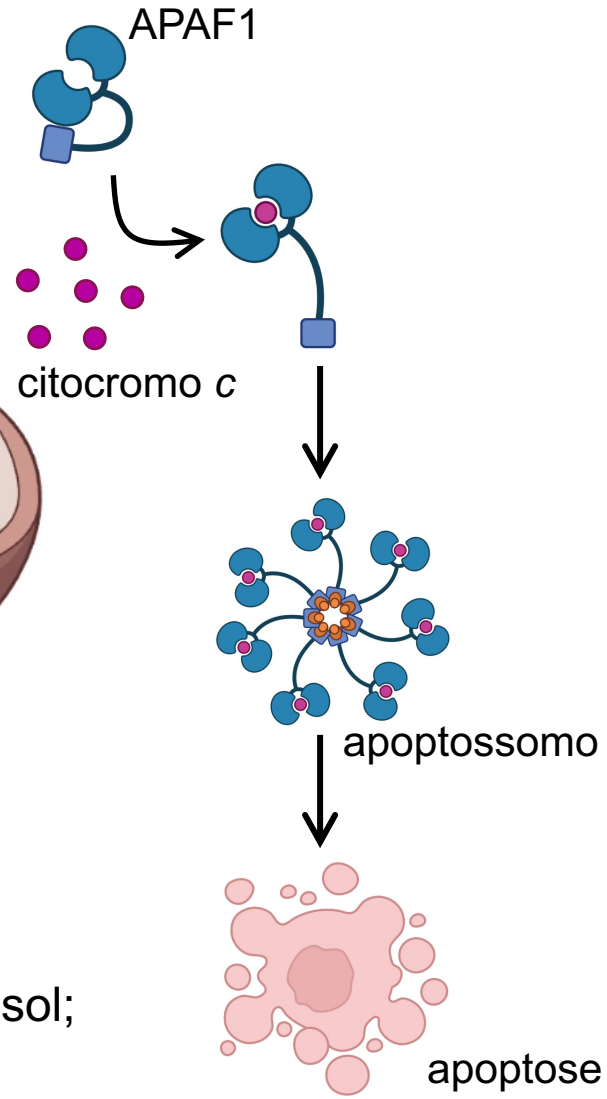
↓ O_2 e ATP

Reperfusão

↑ O_2 e glicose



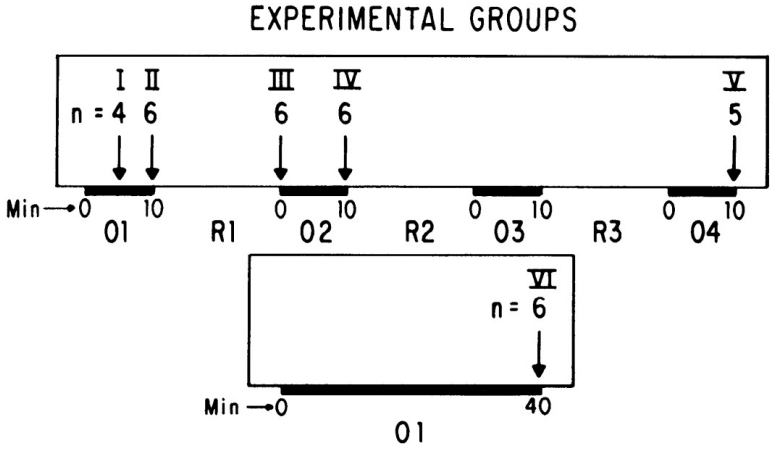
Abertura mPTP;
desregulação cálcio citosol;
morte celular



Pré-condicionamento isquêmico

Four brief periods of myocardial ischemia cause no cumulative ATP loss or necrosis

KEITH A. REIMER, CHARLES E. MURRY, IKUHIRO YAMASAWA,
MARY L. HILL, AND ROBERT B. JENNINGS
Department of Pathology, Duke University Medical Center, Durham, North Carolina 27710

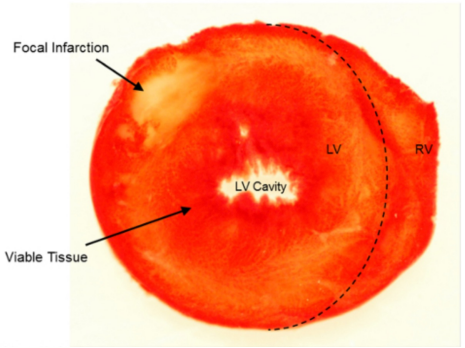


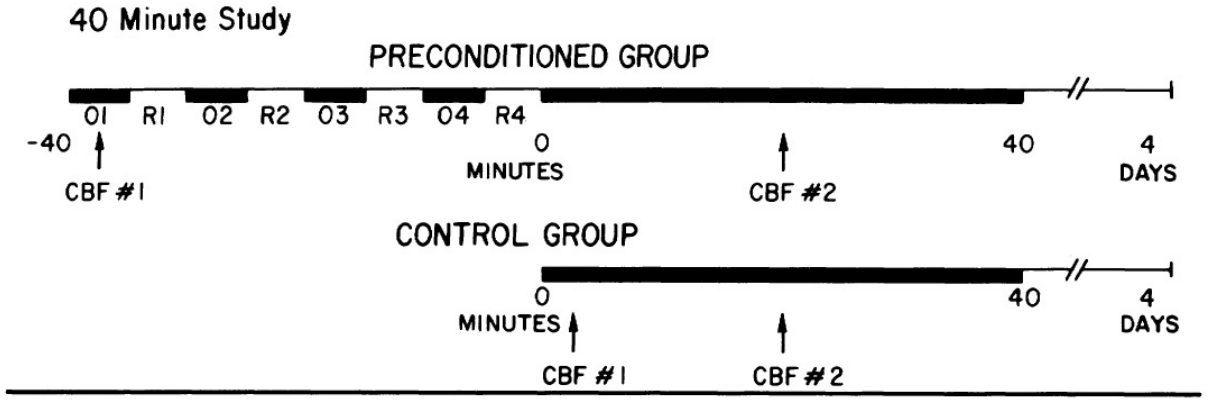
Pré-condicionamento isquêmico

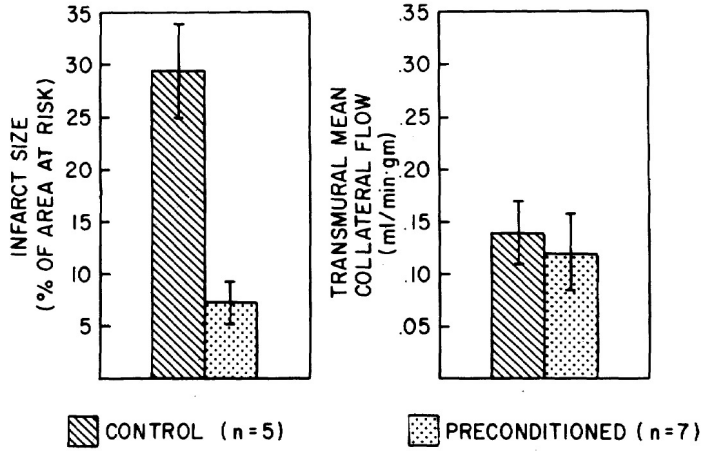
LABORATORY INVESTIGATION
MYOCARDIAL INFARCTION

Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium

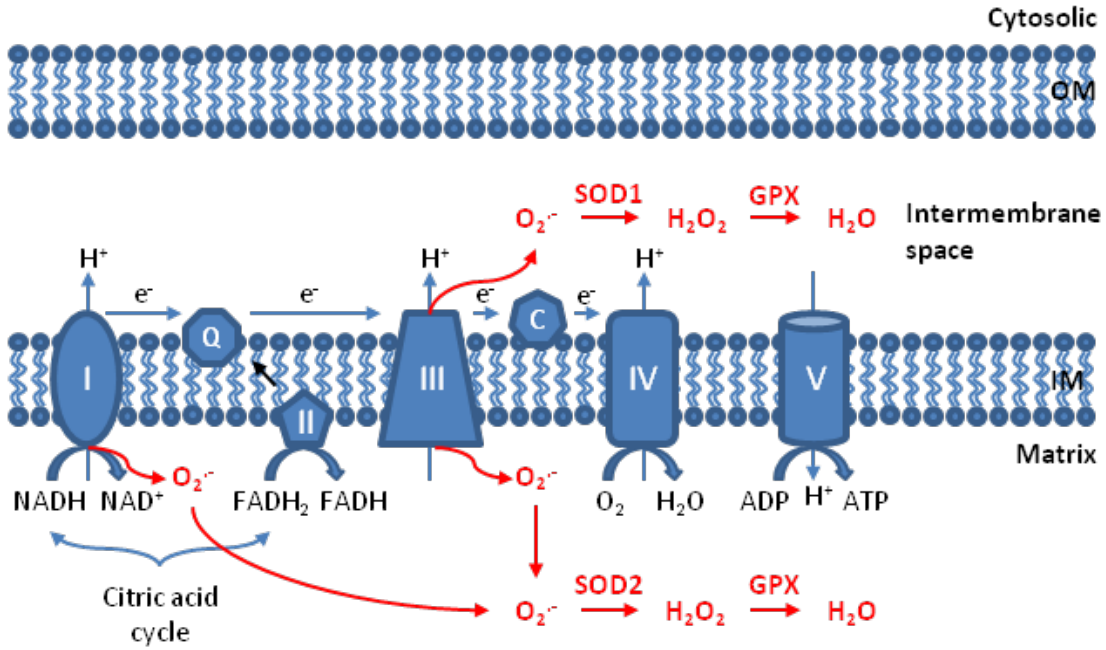
CHARLES E. MURRY, B.S., ROBERT B. JENNINGS, M.D., AND KEITH A. REIMER, M.D., PH.D.







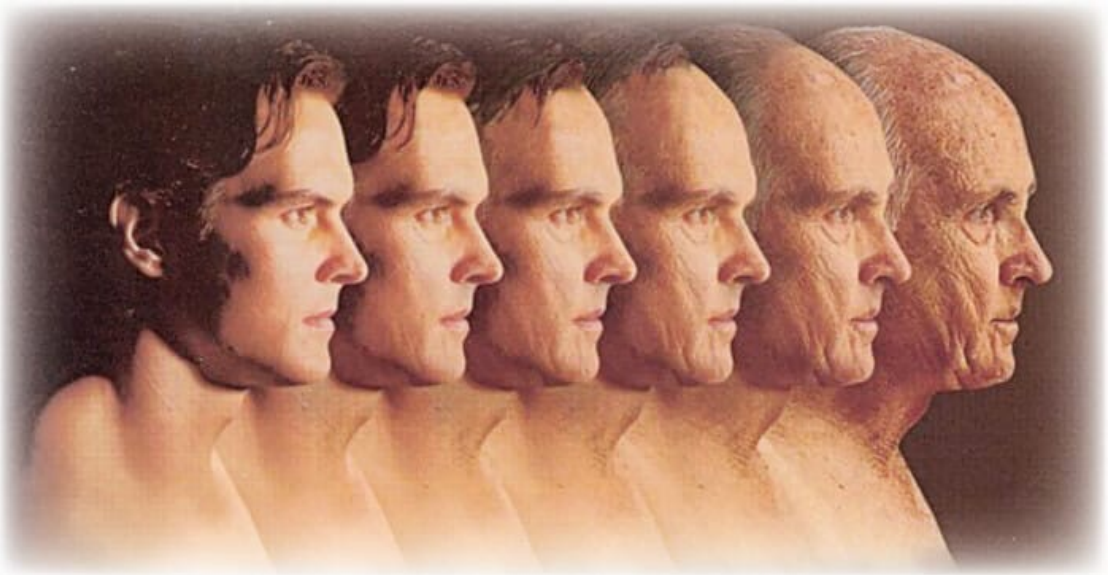
Mitohormesis

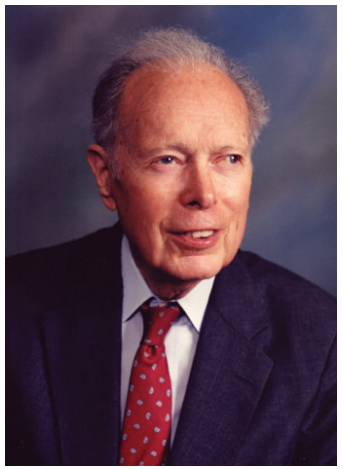


Antioxidantes

Espécies reativas de oxigênio (EROs) ⊣ Resiliência; Expectativa de vida

Envelhecimento

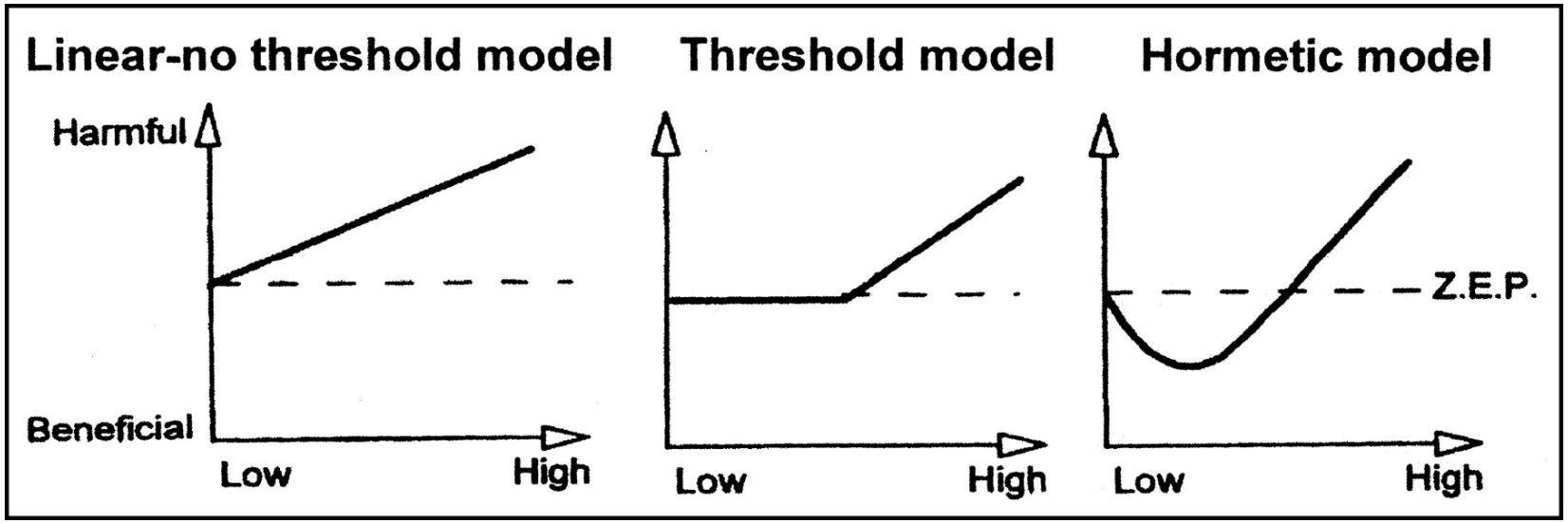




Denham Harman
MD/PhD

Free Radical Theory of
Aging

Hormese



Prekeges, J Nucl Med Tech, 2003

Pré-condicionamento do envelhecimento

Article

Developmental ROS individualizes organismal stress resistance and lifespan

https://doi.org/10.1038/s41586-019-1814-y
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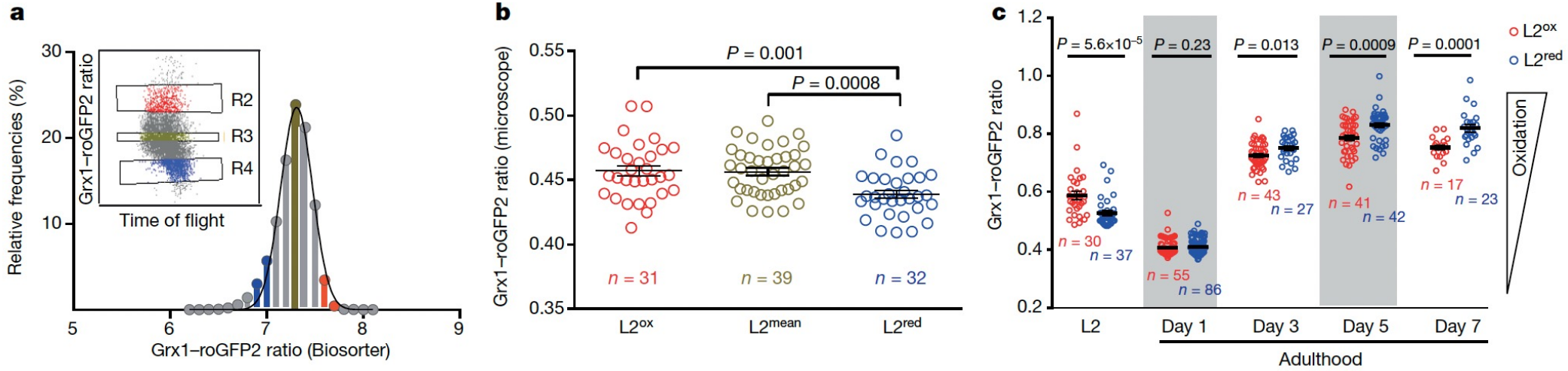
Accepted: 18 October 2019

Daphne Bazopoulou[1], Daniela Knoefler[1], Yongxin Zheng[2,3], Kathrin Ulrich[1], Bryndon J. Oleson[1], Lihan Xie[1], Minwook Kim[1], Anke Kaufmann[1], Young-Tae Lee[4], Yali Dou[4], Yong Chen[5], Shu Quan[2,3] & Ursula Jakob[1]*

Separação de populações
Reduzida vs **Oxidada**



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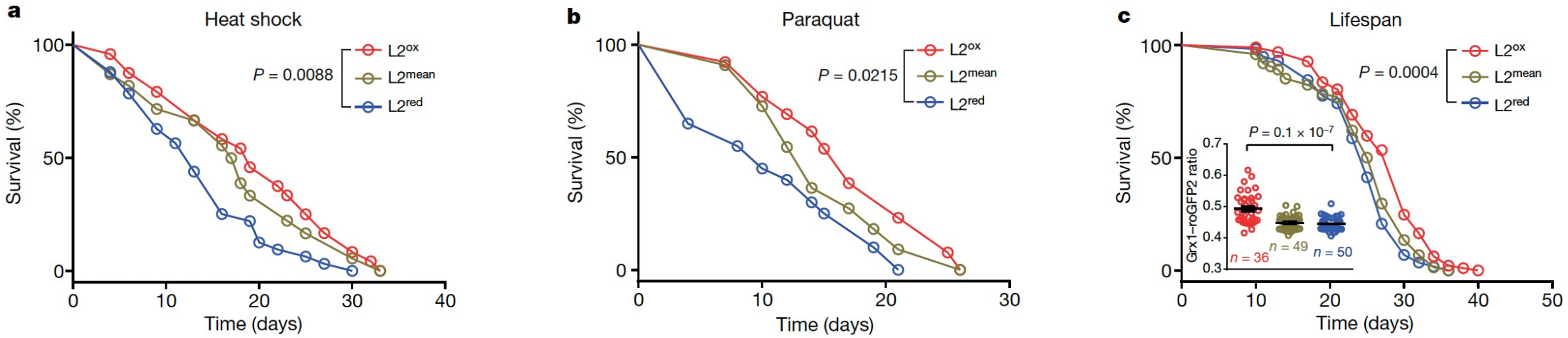
Resistência ao Estresse e Longevidade

Reduzida vs **Oxidada**



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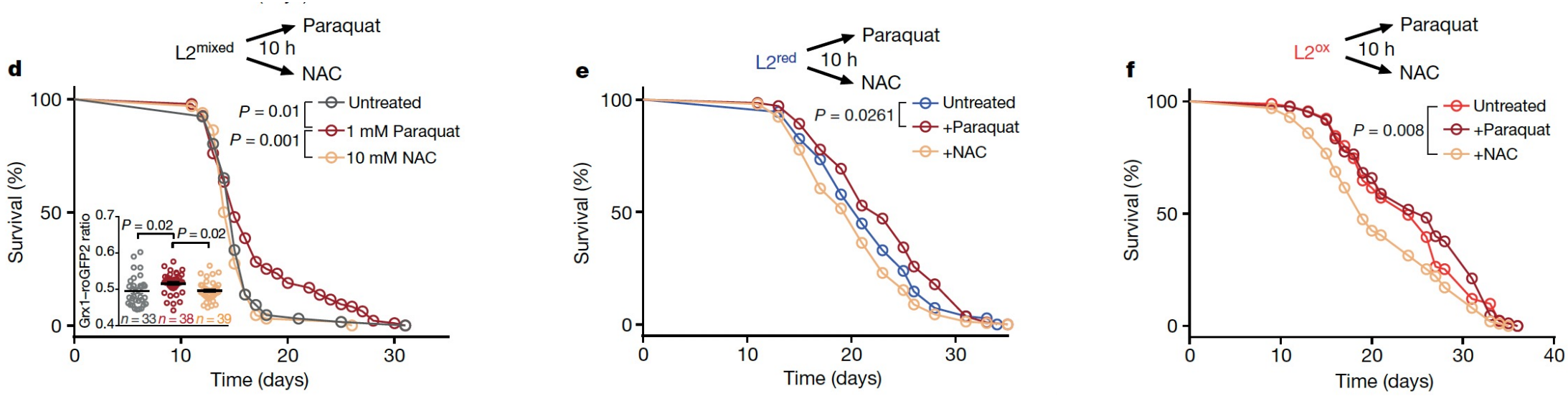
Plasticidade Adaptativa

Reduzida vs **Oxidada**



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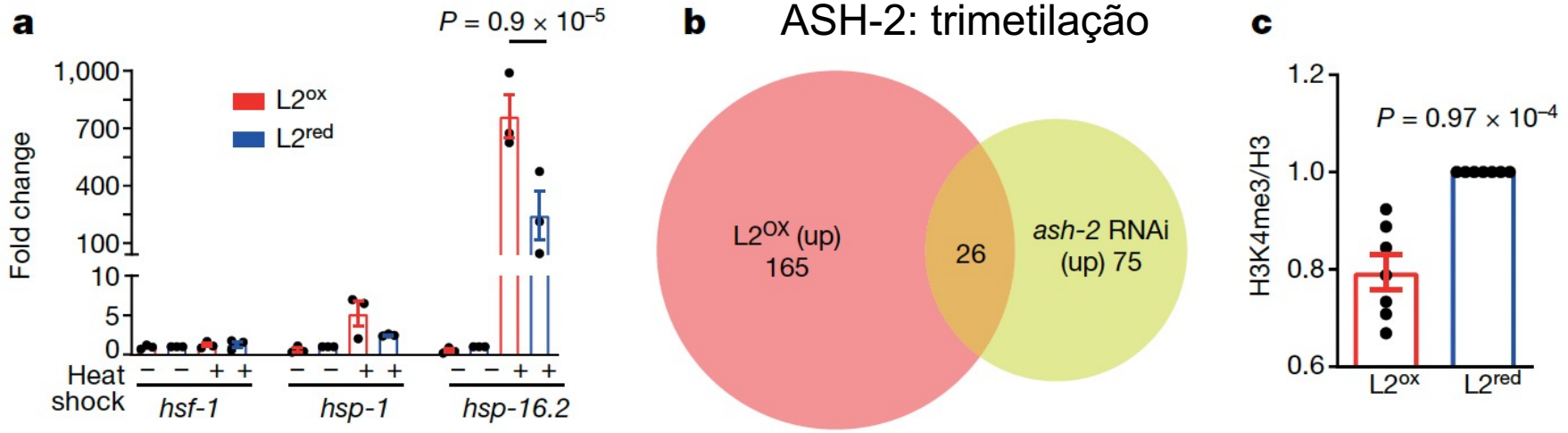
Análise Molecular

Reduzida vs **Oxidada**



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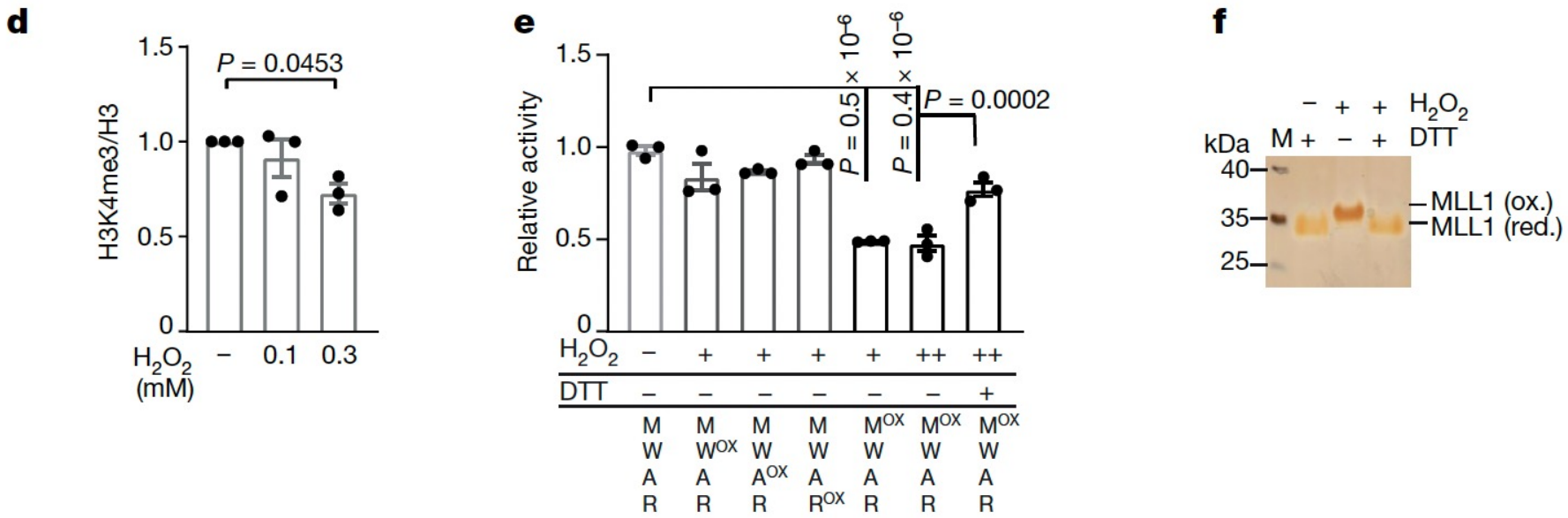
Sensibilidade do Sistema
H3K4me3 a oxidantes
MLL1 (M), WDR5 (W), ASH2L (A) e RBBP5 (R)



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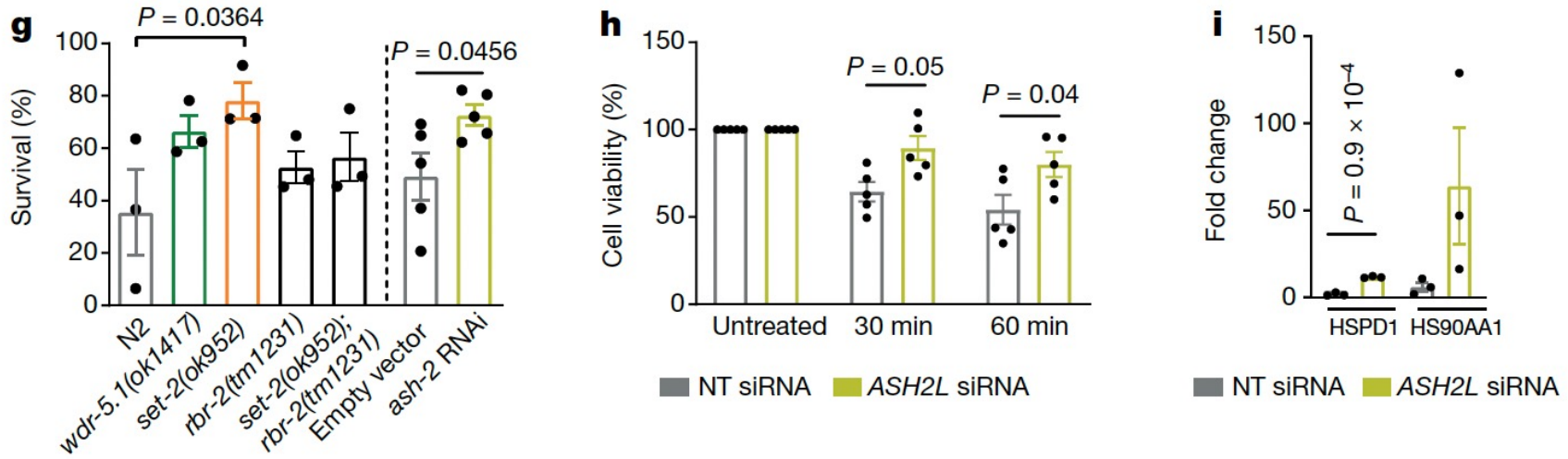
Bloqueio do Sistema **H3K4me3** aumenta a resistência ao estresse celular



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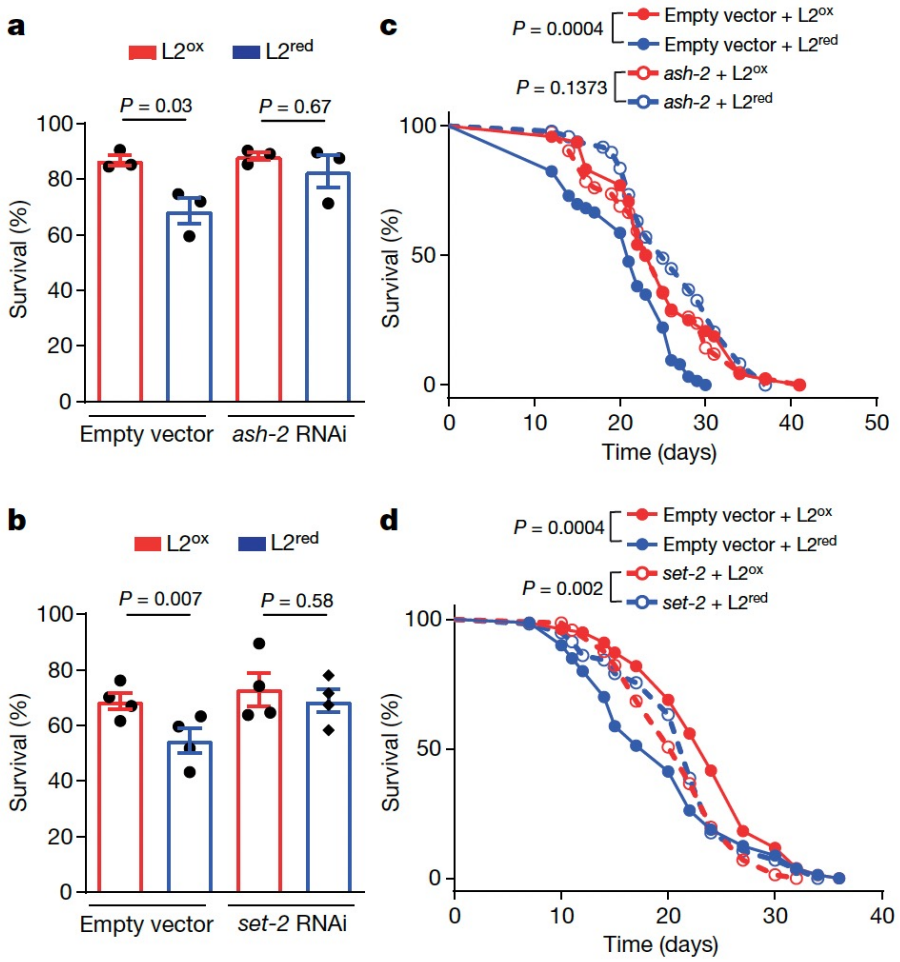
Prova do 9!!!

Transformação do fenótipo do Reduzido em Oxidado



Determinantes do envelhecimento

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Article | Published: 04 December 2019

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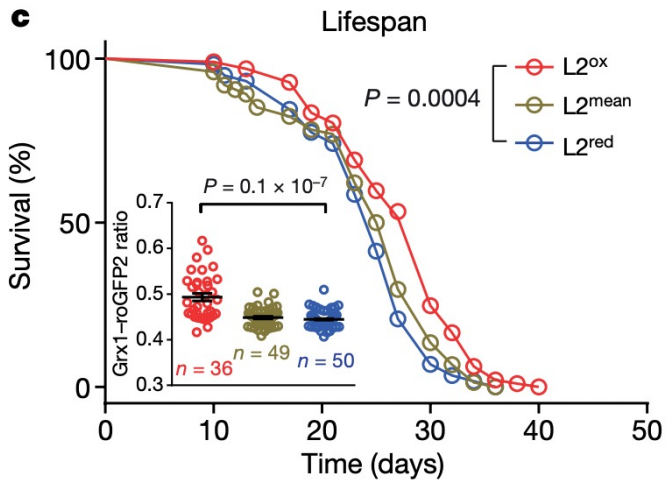
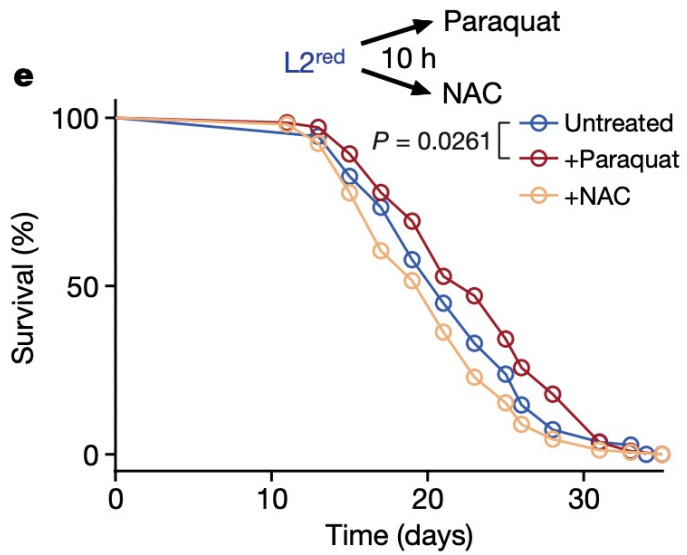
Nature **576**, 301–305 (2019) | Cite this article

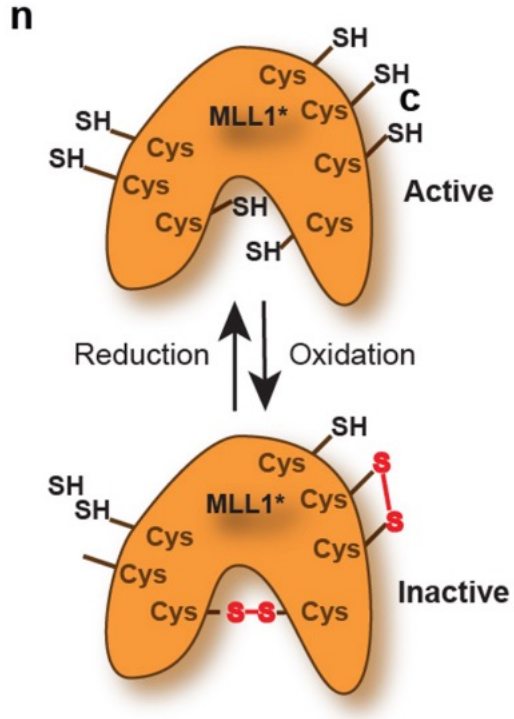
23k Accesses | **75** Citations | **355** Altmetric | Metrics

Controle epigenético

↓ H3K4me3







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Espécies reativas de oxigênio como mensageiros celulares?

Características:

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Acoplamento a sistemas enzimáticos? SOD; Peroxidases

Inespecificidade

Oxidant	Reduction potential ($E^{o\prime}$, V)	k_{GSH} ($M^{-1}\ s^{-1}$)[c]
Radicals (one electron)[a]		
$NO^{\bullet}/{}^{3}NO^{-}$	-0.80	non detectable
$RS^{\cdot}/RS^{-}$ (Cys)	0.92	8.0×10^{8}
$O_2^{\bullet-}, 2H^{+}/H_2O_2$	0.94	~10 to 10^{3}
$HO_2^{\bullet-}, H^{+}/H_2O_2$	1.06	n.d.
$ROO^{\bullet}, H^{+}/ROOH$	1.00	n.d.
$NO_2^{\bullet}/NO_2^{-}$	1.04	3.0×10^{7}
$RO^{\bullet}, H^{+}/ROH$	1.60	n.d.
$CO_3^{\bullet-}, H^{+}/HCO_3^{-}$	1.78	4.6×10^{7}
$O_3^{\bullet-}, 2H^{+}/H_2O, O_2$	1.80	7.0×10^{7}
$HO^{\bullet}, H^{+}/H_2O$	2.31	1.0×10^{10}
Non-radicals (two electron)[b]		
$ONOOH, H^{+}/NO_2^{-}, H_2O$	1.40	6.6×10^{2}
$HOCl, H^{+}/Cl^{-}, H_2O$	1.28	3.0×10^{7}
$H_2O_2, 2H^{+}/2\ H_2O$	1.77	0.9

REATIVIDADE ↓

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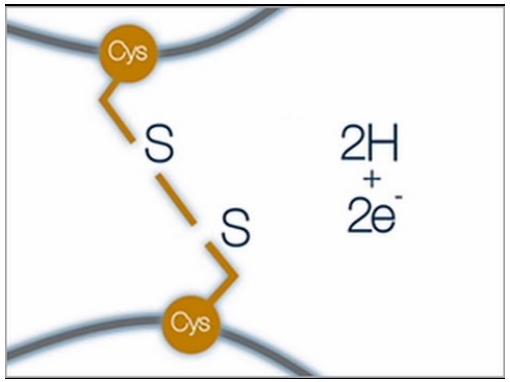
Espécies reativas de oxigênio como mensageiros celulares?

A versatilidade da química dos tióis



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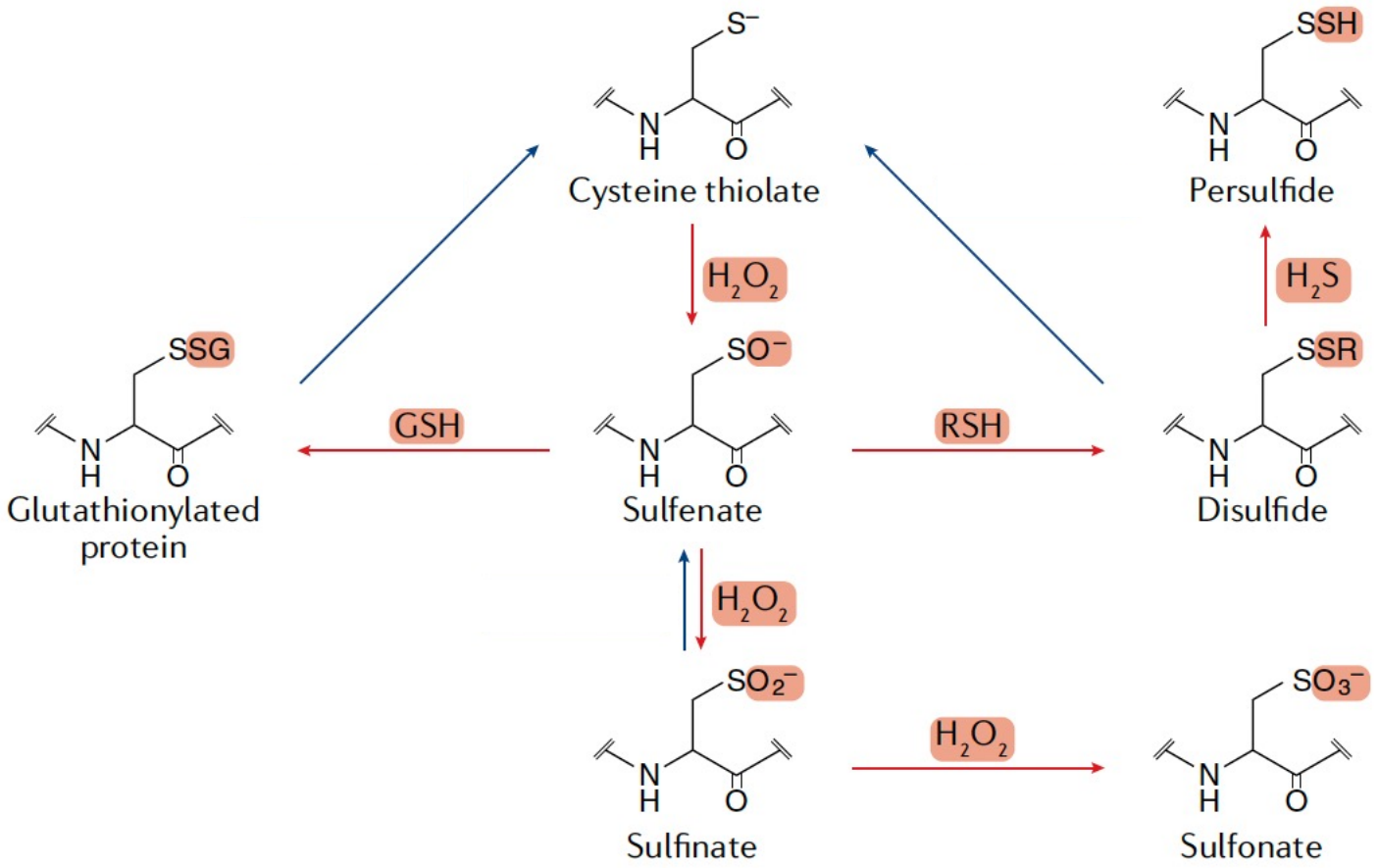
- ✓ Cinética rápida
- ✓ Reversibilidade

-Resíduos de cisteína que participam de ligações dissulfeto são os mais conservados do proteoma

-10-20% dos resíduos de cisteína do proteoma podem ser oxidados

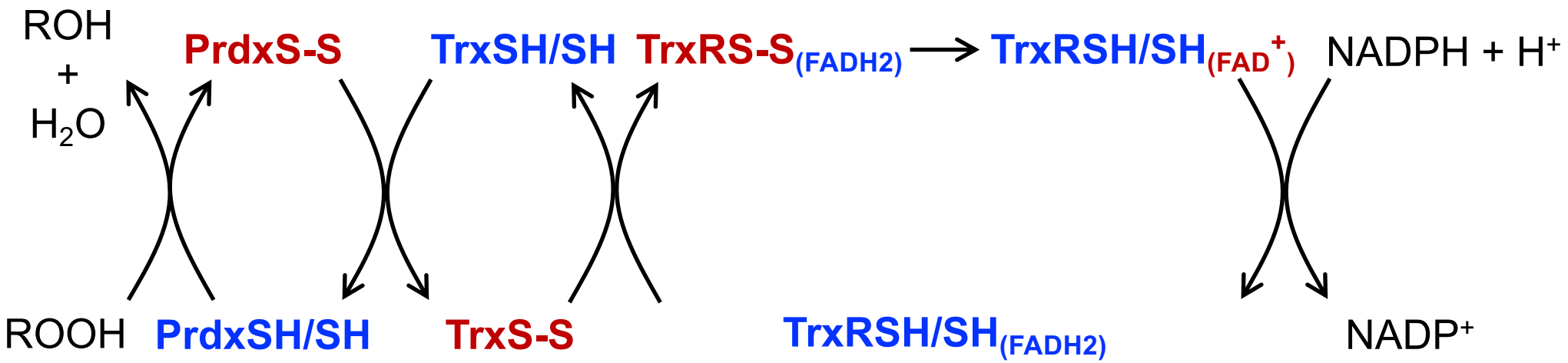
-A complexidade dos organismos aumenta com o conteúdo de ligações de dissulfeto no proteoma

A diversidade química gerada na oxidação de tióis biológicos

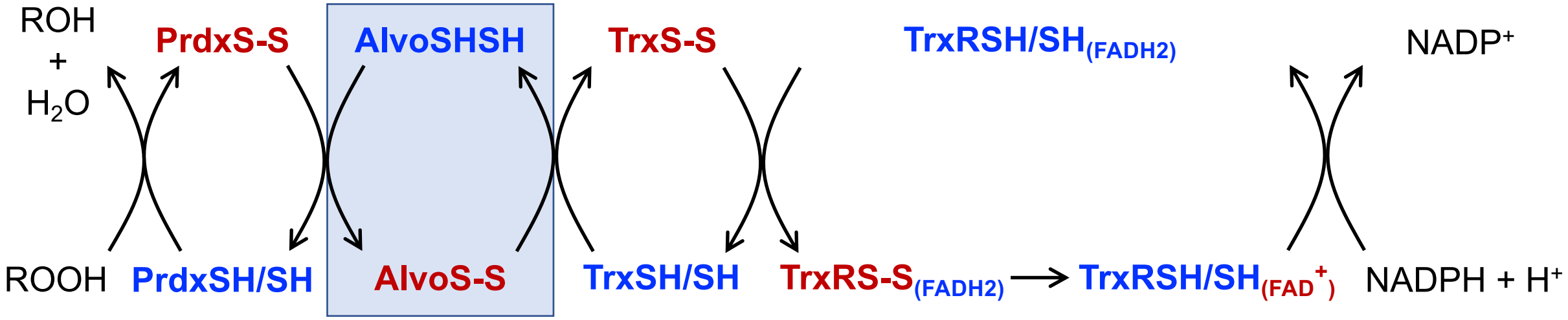


Sies e Jones, Nat Rev Mol Cel Biol, 2020

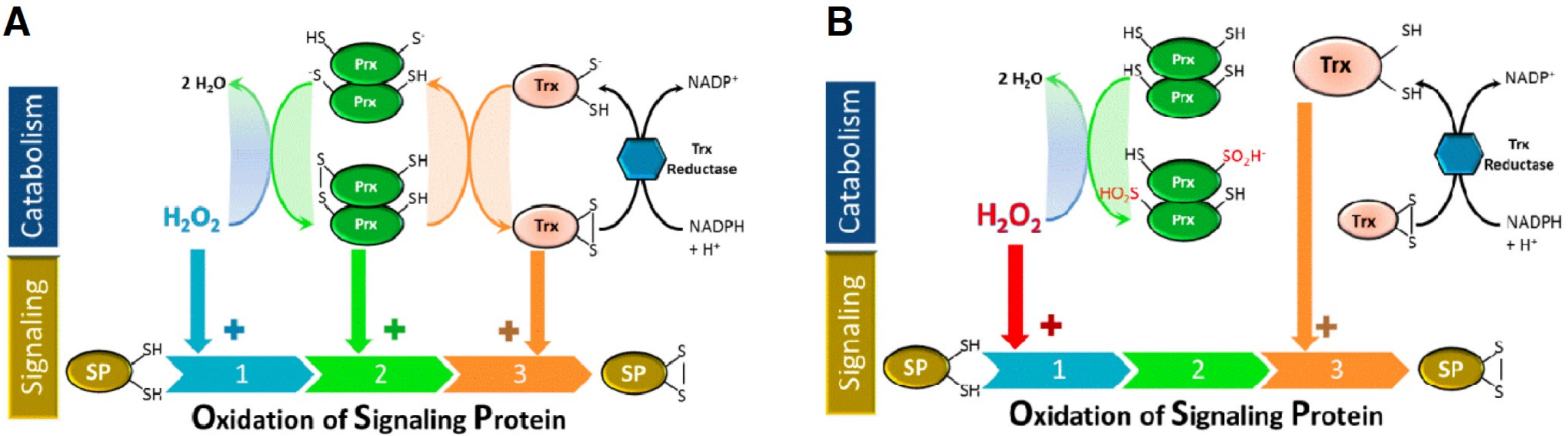
Relé ou Retransmissão Redox



Relé ou Retransmissão Redox



Transdução de sinal pelo H_2O_2

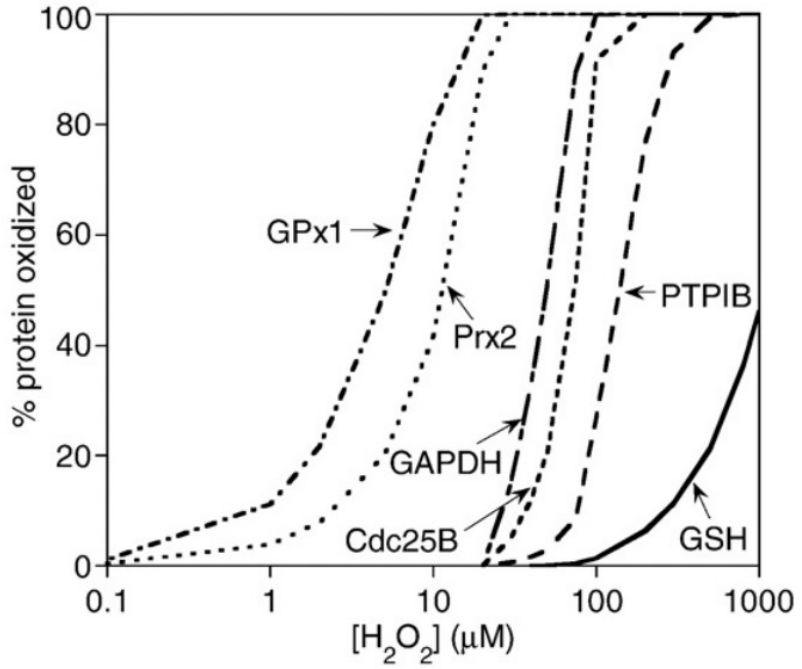


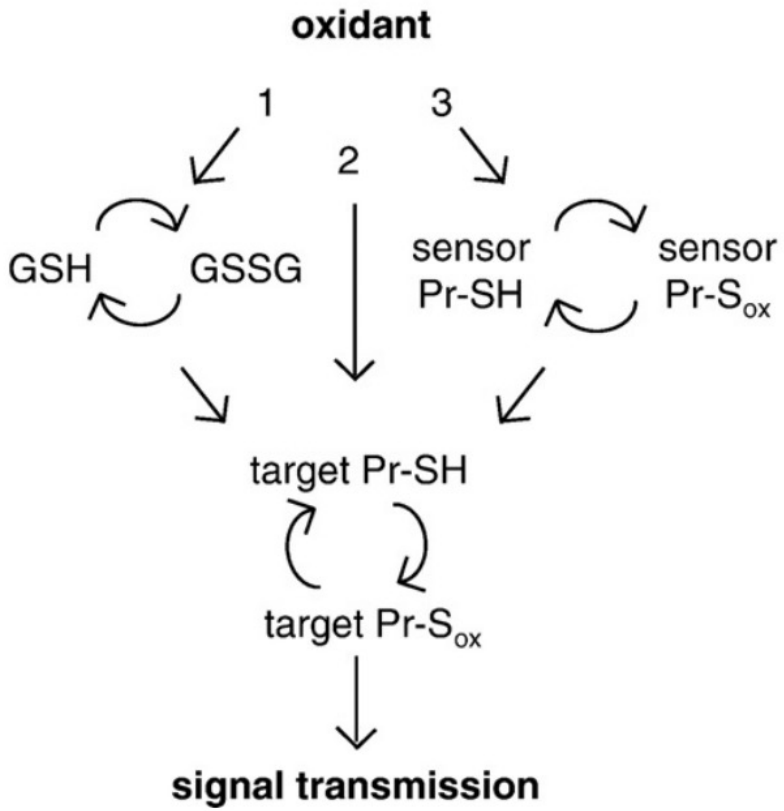
Netto e Antunes, Mol and Cells, 2016

Em eucariotos – Proteina Tirosina Fosfatases

Table 3
pK_a values and reaction rates with hydrogen peroxide for selected low molecular weight thiols and thiol proteins

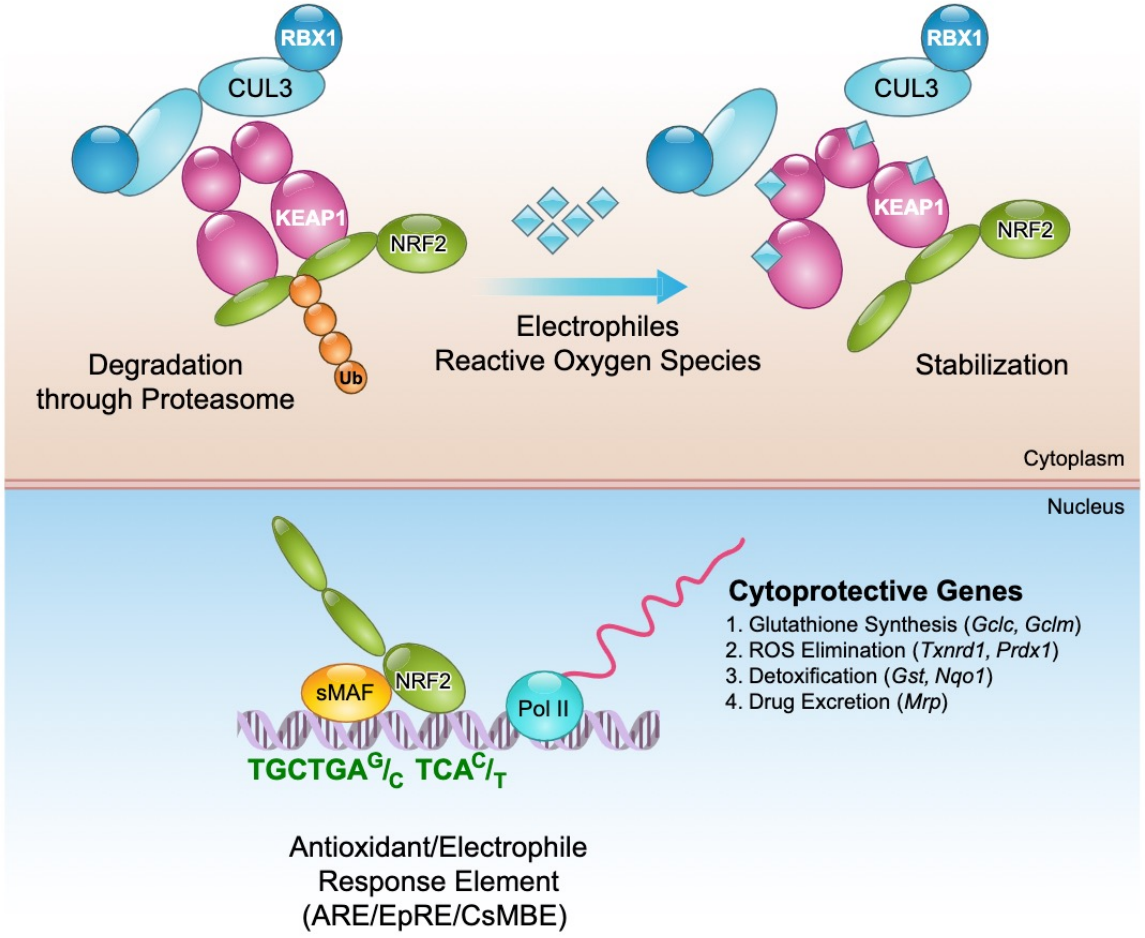
Thiol	pK_a	Rate constant (M^{-1} s^{-1})[a]
GSH	8.8	0.89
Cysteine	8.3	2.9
N-Acetylcysteine	9.5	0.16
Thioredoxin	6.5	1.05
GAPDH[b]	8.2	~500
PTP1B	5.4	20
Cdc25B	6.1	160
Peroxiredoxins	5–6	1–4 × 10^7





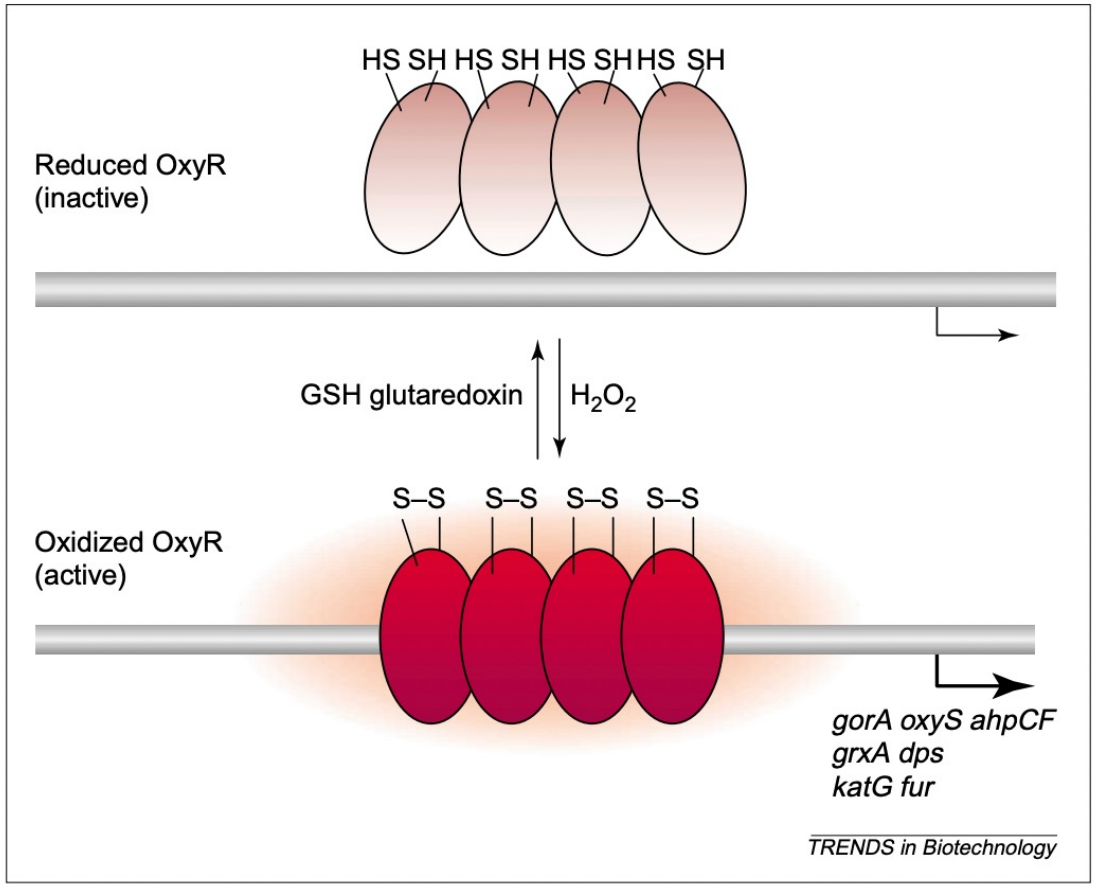
Winterbourn e Hampton, FRBM, 2008

NRF-2 e a resposta antioxidante em eucariotos

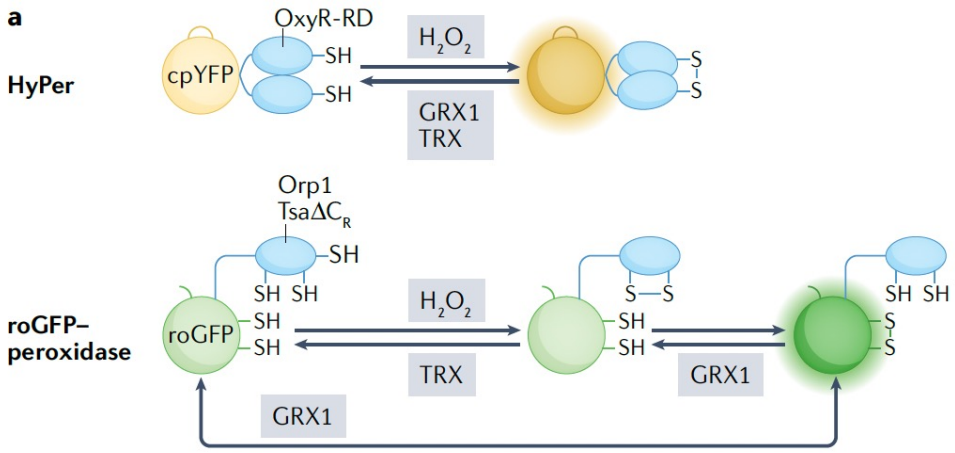


Yamamoto e colabs, Physiol Rev, 2018

Em bactérias



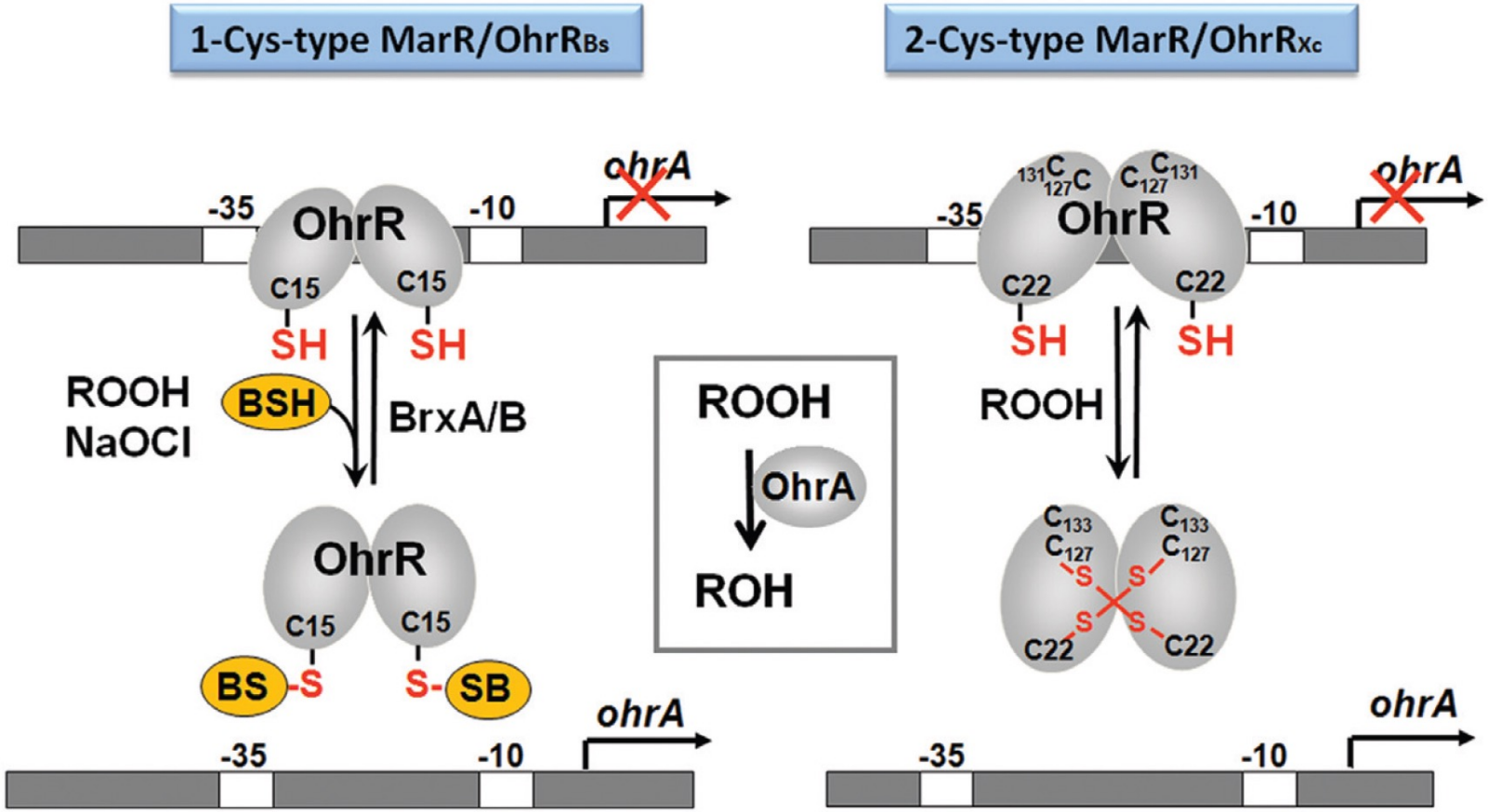
Pomposiello e Demple, Trends in Biotechnol, 2001



Sies e colabs, Nat Rev Mol Cell Biol, 2022

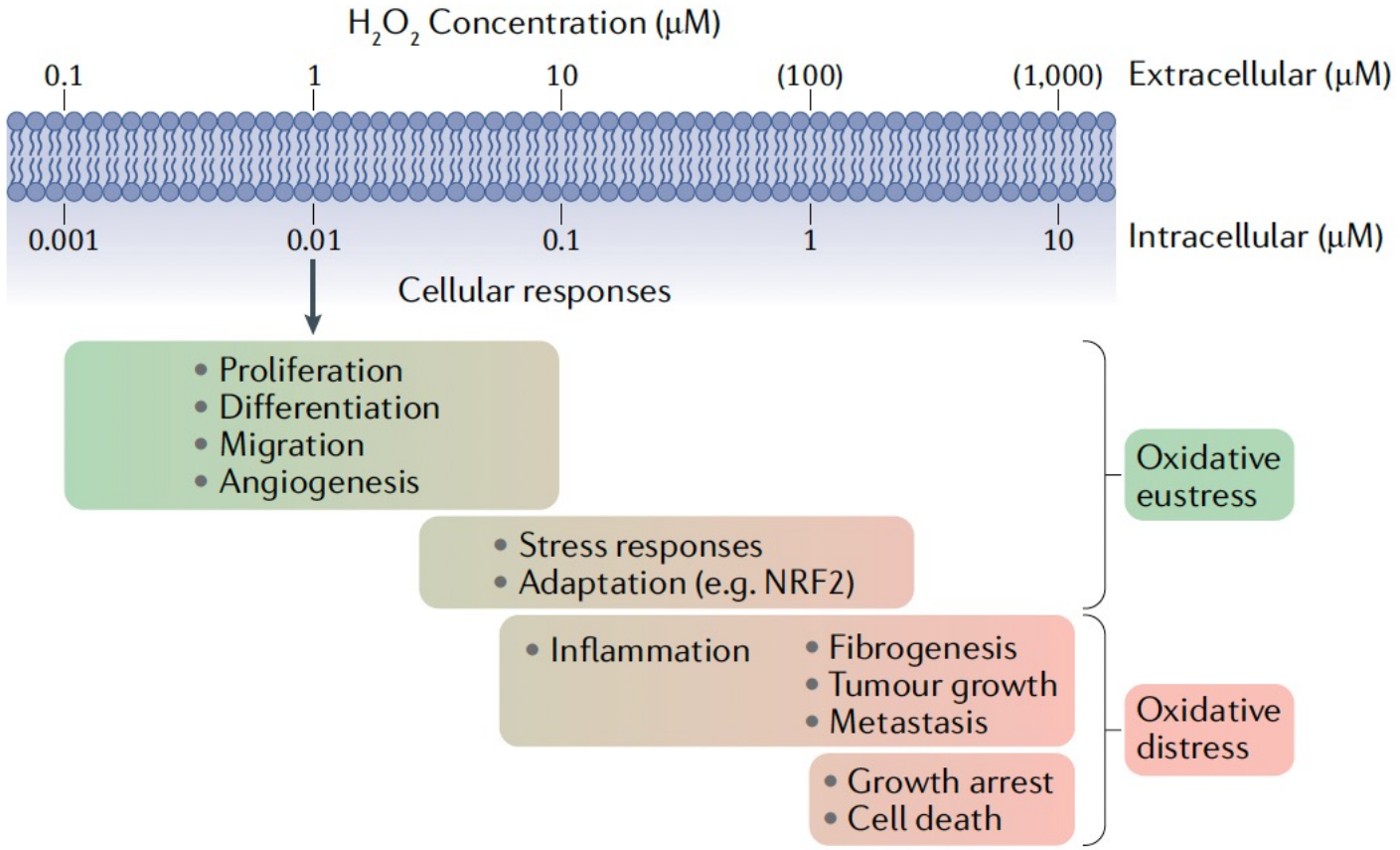
Em bactérias

Resposta a hidroperóxidos de lipídeos



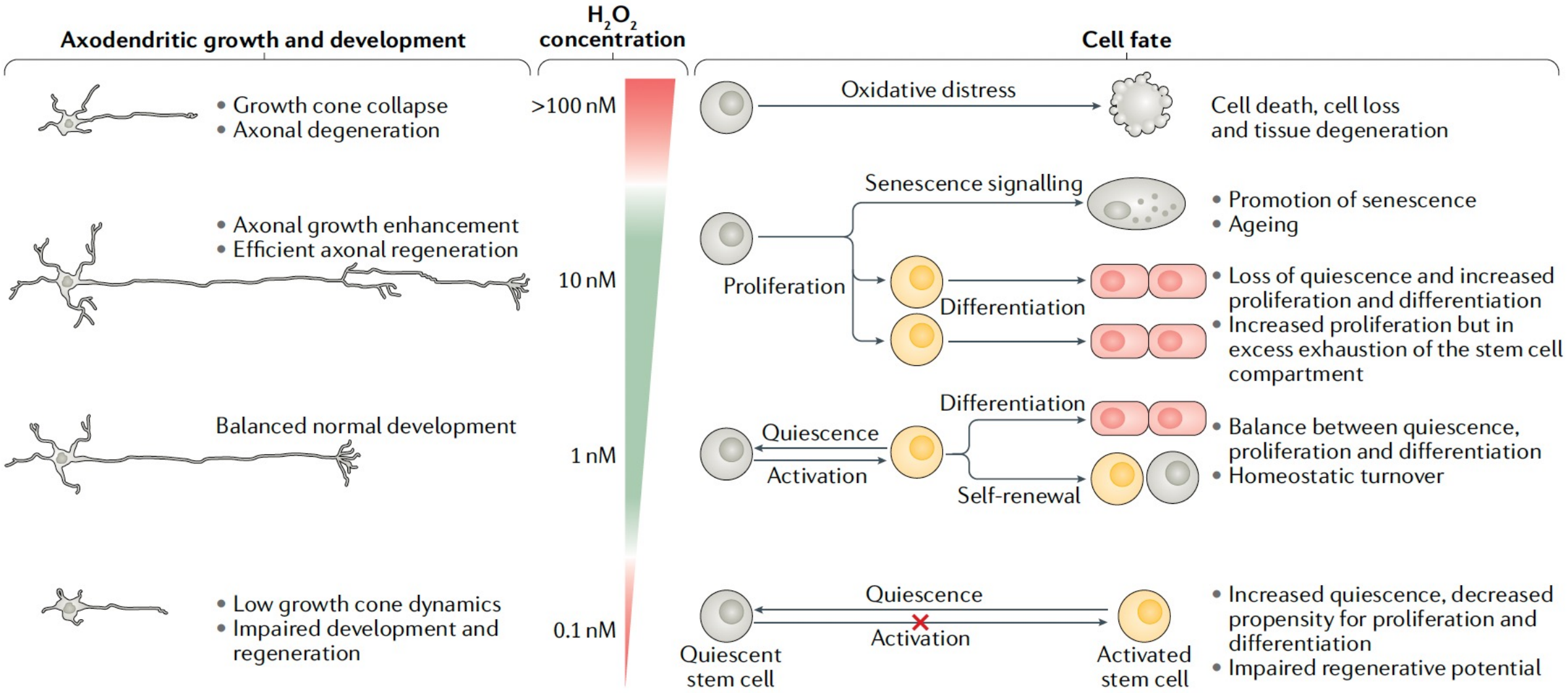
Hillion e Antelmann, Biol Chem, 2015

Concentrações de H_2O_2 e seus efeitos biológicos



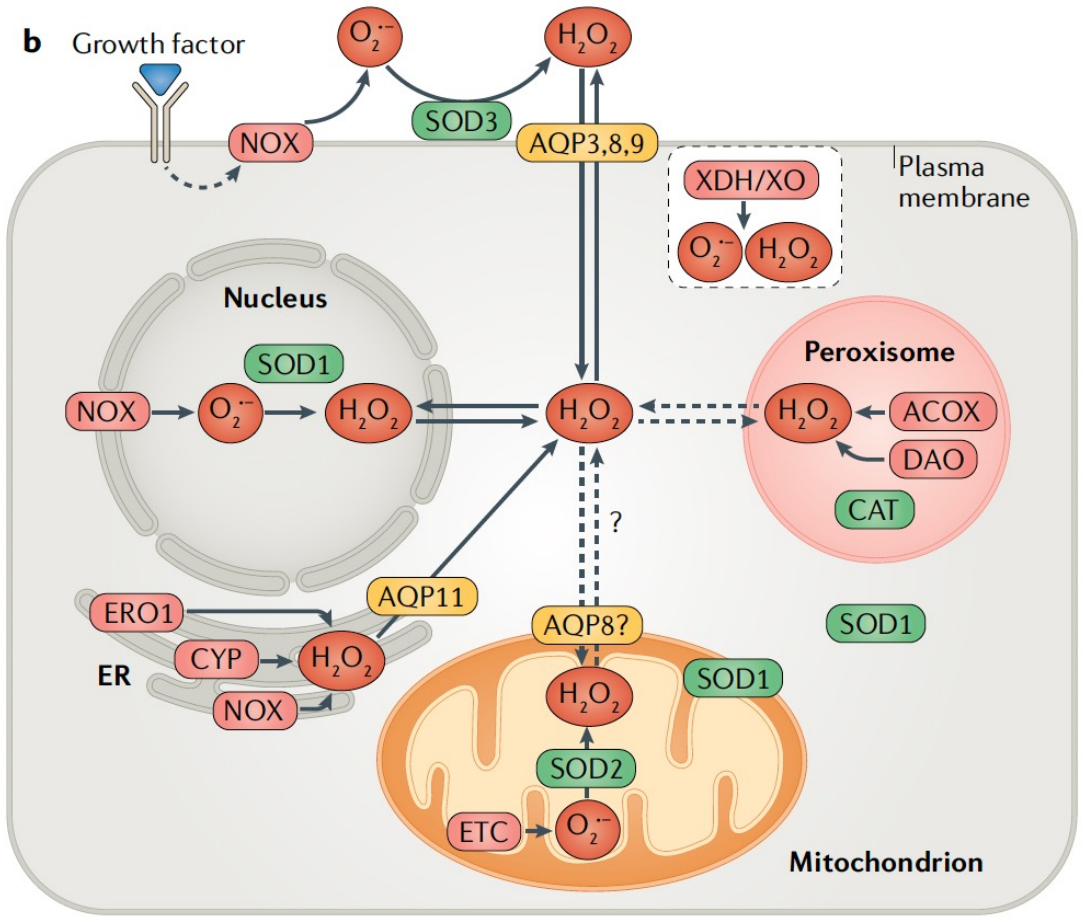
Sies e Jones, Nat Rev Mol Cel Biol, 2020

Concentrações de H_2O_2 e seus efeitos biológicos



Sies e Jones, Nat Rev Mol Cel Biol, 2020

Onde é produzido o H_2O_2



Sies e Jones, Nat Rev Mol Cel Biol, 2020

Oximouse- uma plataforma para estudar sinalização redox revela motivos estruturais

Cell

Article

A Quantitative Tissue-Specific Landscape of Protein Redox Regulation during Aging

Haopeng Xiao,[1,2,5] Mark P. Jedrychowski,[1,2,5] Devin K. Schweppe,[2] Edward L. Huttlin,[2] Qing Yu,[2] David E. Heppner,[1,3] Jiaming Li,[2] Jiani Long,[4] Evanna L. Mills,[1,2] John Szpyt,[2] Zhixiang He,[3] Guangyan Du,[3] Ryan Garrity,[1] Anita Reddy,[1,2] Laura Pontano Vaites,[2] Joao A. Paulo,[2] Tinghu Zhang,[1,3] Nathanael S. Gray,[1,3] Steven P. Gygi,[2] and Edward T. Chouchani[1,2,6,*]

[1]Department of Cancer Biology, Dana–Farber Cancer Institute, Boston, MA, USA
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[5]These authors contributed equally
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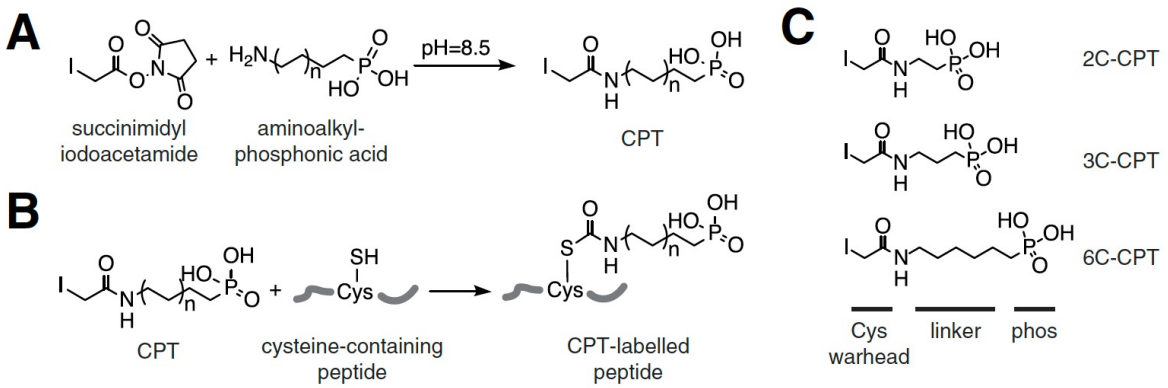
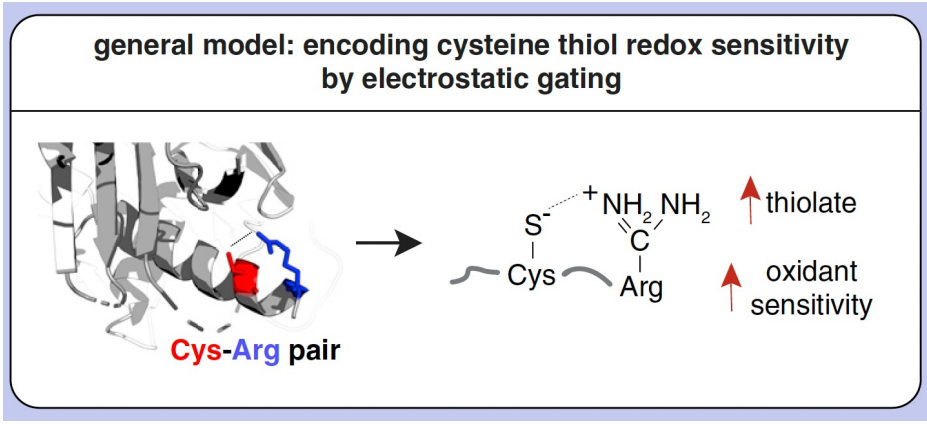
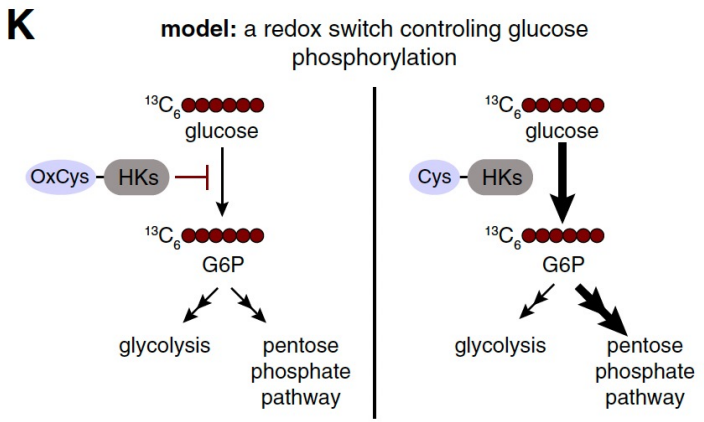
https://doi.org/10.1016/j.cell.2020.02.012

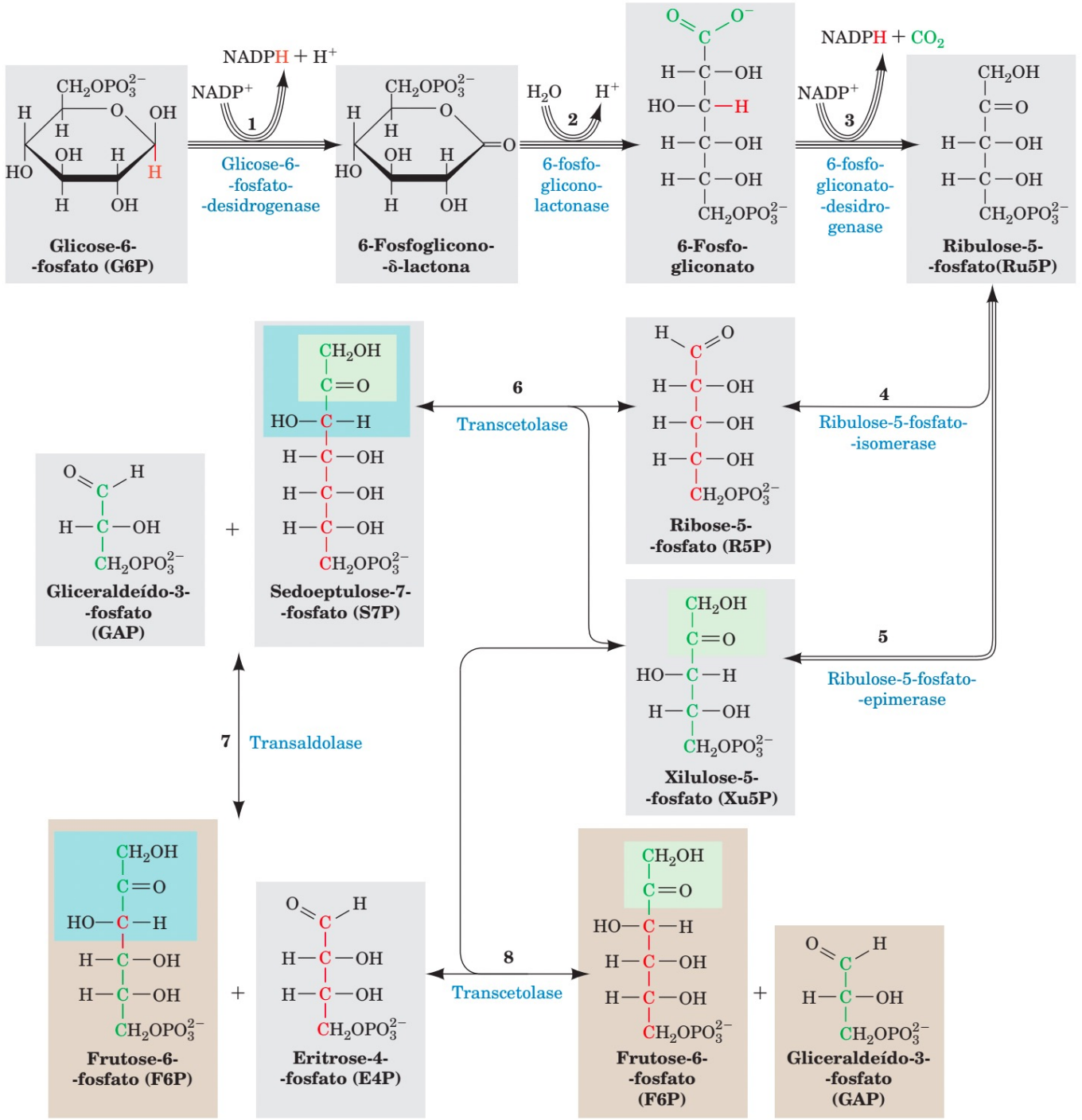




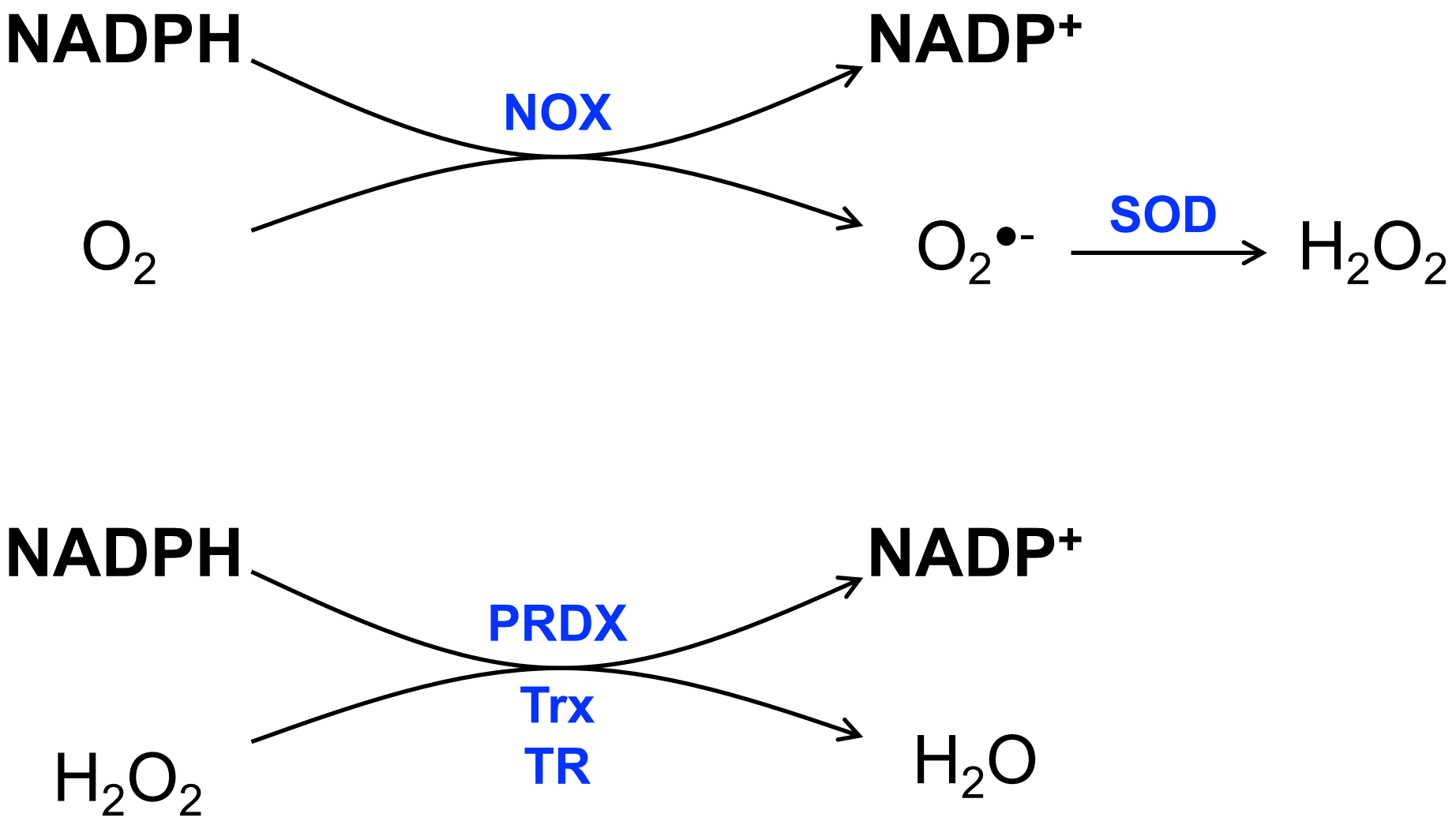


O envelhecimento remodela redes regulatorias redox globalmente em camundongos

Via das Pentoses



NADPH: via de acoplamento entre a geração e a eliminação de oxidantes?



Fosforilações

Oxidações

Fosforilações

A sinalização redox está acoplada ao metabolismo energético?

Oxidações

Fosforilações

Oxidações

Recapitulando as metas da aula

- Considerações sobre sinalização celular.
- Indícios para o papel de oxidantes em respostas biológicas.
- Tipos de oxidantes de podem funcionar como mensageiros.
- Mecanismos bioquímicos da sinalização redox.
- Sinalização redox exemplificada e sua conexão com o metabolismo energético.

Bibliografia

- Halliwell and Gutteridge, Free Radicals in Biology and Medicine, 5th Edition, 2015.
- Manuscritos citados.

Atividades extracurriculares

- https://oximouse.hms.harvard.edu/

Questões de Acompanhamento

1. Explique mecanismos de adaptação celular ao estresse oxidativo.

2. Discuta as características do H_2O_2 no meio biológico que o tornam um bom mensageiro celular.

3. O que são relés redox? Exemplifique.

4. Discuta vias de sinalização redox que afetam a expressão genica.

5. Explique o possível acoplamento da sinalização redox com o metabolismo energético.